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(54) Title: SELECT AMINO ACIDS AS ZINC-SOLUBILIZING AGENTS IN ANTI-VIRAL GENITAL FORMULATIONS

(57) Abstract: Formulations including zinc gluconate and select amino acids for use on genital surfaces to help prevent the spread of sexually transmitted diseases are disclosed. The select amino acids are glycine, arginine, and/or lysine. These formulations are generally applied shortly before sexual intercourse. When used in this manner, the formulations provide a non-toxic, non-irritating chemical protective layer that reduces the risk of viral transmission from an infected person to an uninfected person.

SELECT AMINO ACIDS AS ZINC-SOLUBILIZING AGENTS IN ANTI-VIRAL GENITAL FORMULATIONS

FIELD OF THE INVENTION

The invention relates to anti-viral genital formulations which include zinc salts as anti-viral agents and select amino acids, such as L- or D,L-alanine (hereinafter "alanine"), glycine, or L- or D,L-lysine (hereinafter "lysine"), to increase the solubility of the zinc salts in the formulations. The formulations are preferrably in the form of an ointment, a gel or the like. The formulations are particularly useful as a genital lubricant for use prior to and during intercourse to reduce the infectivity of one or more sexually transmitted diseases.

BACKGROUND OF THE INVENTION

During the past years, the need for lubricant formulations or other formulations that can be applied to the surface of the genitals and used during intercourse to help slow the spread of sexually transmitted diseases has become increasingly apparent. For a number of reasons (including low rates of condom use among people at risk; patterns of high-risk behavior among adolescents, drug users, and others; the absence of effective vaccines against most sexually transmitted viruses; and the development of drug combinations that can reduce the blood-borne viral loads of HIV-infected patients but which cannot cure them of the infection), additional alternatives are needed to help slow the spread of sexually transmitted viruses.

As used herein, "genital lubricant formulations" refers to formulations that are spread across one or more surfaces of the genitals, and that remain in contact with genital surfaces during sexual intercourse. The formulations that are of interest herein are normally applied shortly before sexual intercourse, and should remain directly in contact with the genital surfaces throughout the entire act of intercourse. When used in this manner, they can provide a non-toxic, non-

irritating chemical protective layer that helps reduce the infectivity of any sexually transmissible virus that either person might have.

It must be emphasized that the formulations of the invention are intended to reduce the risk of infection in a person who has not been previously infected by a particular type of virus. The formulations are not intended as treatments for people who are already infected by such viruses. The formulations are not intended to reduce viral concentrations in blood or tissue, or to reduce the severity or frequency of any symptoms of an already established viral infection. Instead, the formulations are intended to reduce the risk of viral transmission from an infected person to an uninfected person, during or immediately after sexual intercourse.

Genital lubricant formulations are normally and preferably in fluidized form, so that they can also serve as lubricants, to minimize any genital irritation during sexual intercourse. Such lubricating activity can help promote and encourage consistent use during each act of intercourse and thus to maximize the efficacy of anti-viral agents contained therein for reducing the risk of infection. Such fluidized lubricants include aqueous gels, which are normally sold in plastic tubes and single-use sealed packets (such as K-Y Lubricating Jelly™, sold by Johnson & Johnson, New Brunswick, NJ), and pourable lotions or ointments (such as AstroGlide™, sold by Ansell, Eatontown, NJ). Such formulations can also include fluids that are soluble in water, but which do not themselves contain water (such as condom lubricants, most of which contain silicone compounds such as dimethylsiloxane, but not water).

The role of various zinc salts as potential anti-viral agents in genital lubricants is described in U.S. Patent Nos. 5,208,031; 5,482,053; 5,545,673; 5,599,551; 5,624,675 and 5,785,054, all to Kelly. Each

of these patents, however, teach that zinc gluconate is not a preferred zinc salt for use in a genital lubricant because it is not adequately soluble in water. When tested according to the methods described in the patents, zinc gluconate generated a mixture that contained noticeable levels of grit and abrasive. As stated in several of the above patents, "Zinc gluconate was also tested and did not cause any irritation during intercourse. However, it does not have a high degree of solubility in water, and when extensively ground in a mortar and pestle and then mixed thoroughly in a gel, the gel contained very fine, small particles which displayed a very slight roughness when rubbed hard between the forefinger and thumb. Although no abrasion or irritation was noticeable by either person during intercourse, it is not recommended for use in a lubricant, due to the risk of creating microabrasions that might help viral particles penetrate skin or mucous membranes."

The above-quoted passage, and other similar passages, are contained at column 9, lines 4-14 of U.S. Patent No. 5,545,673 (also see Example 3, in column 15) column 8, line 62-column 9, line 4 of U.S. 5,482,053; and column 10, lines 1-11 of U.S. Patent No. 5,785,054. Also see Example 3 in U.S. Patent Nos. 5,208,031 and 5,599,551.

Thus, a problem with zinc gluconate was explicitly identified in these patents and no solution to the problem was recognized as being known. This is regrettable since zinc gluconate is otherwise very well suited for biological and nutritional use. Zinc gluconate is known for use as a nutritional mineral supplement. Further, zinc gluconate is listed as a GRAS ("generally recognized as safe") agent by the U.S. Food and Drug Administration for oral consumption by humans.

In human clinical trials, zinc gluconate has been shown to be effective in suppressing rhinoviruses and other viruses that cause the common cold (Al-Nakib et

al, 1987[2]; Mossad et al, 1996[15]; Novick et al, 1996[16]). Zinc gluconate is used in flavored hard candy lozenges used in treating colds as described in U.S. Patent Nos. 4,684,528 and 4,758,439. When used in such lozenges, zinc gluconate acts as an agent, which directly contacts and acts upon the surfaces of the mucous membranes inside the mouth and is known to have immune-enhancing activity.

OBJECTS AND BRIEF DESCRIPTION OF THE INVENTION

A primary object of the present invention is to provide suitable agents for increasing the solubility of zinc gluconate so that zinc gluconate can be used as an anti-viral agent in genital formulations, such as lubricant gels.

Another object of the invention is to provide genital formulations including zinc gluconate and one or more select amino acids, in particular, glycine, alanine, and/or lysine, to increase the solubility of the zinc gluconate in the genital formulations without causing irritation or other undesired side effect on the genitals, and without blocking the anti-viral activity of the zinc gluconate.

Another object of the invention is to provide a zinc gluconate-amino acid mixture useful in a genital lubricant formulation that has a pleasant odor and a not-unpleasant taste.

Yet another object of the invention is to provide a genital formulation which has a combination of two or more different zinc salts, such as zinc gluconate (solubilized by the addition of a select amino acid, e.g., alanine, glycine and/or lysine) and zinc lactate.

These and other objects of the invention will become more apparent through the brief description of the invention and description of the preferred embodiments.

Genital formulations (in particular lubricant formulations such as aqueous gels) of the invention include zinc gluconate as an anti-viral agent and select

amino acids, in particular alanine, glycine (also called aminoacetic acid) and/or lysine, to increase the solubility of the zinc gluconate in a formulation. These ingredients, used together can provide an anti-viral genital formulation that has a pleasant odor and taste, and which can reduce the risk of infection by sexually transmitted viruses, such as herpes simplex viruses (HSV) and the human immunodeficiency virus (HIV), the causative agent for AIDS. Additional genital formulations of the invention can further include a second zinc salt, such as zinc lactate. This optional zinc salt can reduce the quantity of gluconate ions that are released inside the vagina, and substitute lactate ions instead of gluconate ions. Lactate ions are already present at relatively high concentrations inside the vagina, and the mucous membranes in the vagina and urethra are well-adapted to and highly tolerant of lactate ions.

The zinc gluconate is present in a genital formulation of the invention at a concentration of from about a 0.10 millimolar to about 200 millimolar.

The one or more amino acids is present at a molar ratio to the zinc gluconate of from about 1 to about 50.

DESCRIPTION OF PRESENTLY PREFERRED EMBODIMENTS

The following description is to illustrate the antiviral efficacy of zinc gluconate and zinc lactate by an in vitro demonstration.

Using a standard plaque assay and fresh clinical isolates of herpes simplex virus (HSV), Arens and Travis, (1998)[1] investigated the ability of zinc gluconate and of zinc lactate, both in the presence of two moles of glycine (per mole of zinc), to inactivate HSV. For the assay, a virus was treated by incubating at 37°C with zinc salts in MOPS-buffered culture media and then diluted and plated onto CV-1 cells for detection of infectious virus. Treatment of HSV with an aqueous

solution that was 50 millimolar in zinc gluconate and 100 millimolar in glycine, or with an aqueous solution that was 50 millimolar in zinc lactate and 100 millimolar in glycine, for 5 minutes resulted in 98.8 to 100% loss of infectivity as measured by the plaque assay.

The effect was concentration dependent. Solutions of zinc gluconate or zinc lactate, always containing two molar equivalents of glycine, and containing the zinc salts at 50, 40, and 30 millimolar concentration caused 100% inactivation, while 15 millimolar zinc salts caused 98 to 99% inactivation and 5 millimolar zinc salts caused 63 to 86% inactivation. These results are shown in the sole figure.

The ability of these zinc salts to inactivate HSV was not related to pH in the range of 6.1 to 7.6, since the inactivation by either salt in that pH range was 99.7 to 100% with 50 millimolar zinc salt containing 100 millimolar glycine.

Four HSV-1 and two HSV-2 fresh clinical isolates responded in a similar manner to treatment with either zinc salt solution.

The following illustrates the bacteriological safety of zinc gluconate with glycine and of zinc lactate with glycine.

Glycine is a component of nutrient solutions (growth media) used in the laboratory propagation of a wide variety of bacteria, fungi, and molds. Therefore, in consideration of the inventive use in the zinc formulations described herein, it was necessary to demonstrate that the presence of glycine, along with the zinc salts, does not encourage or promote the growth of microorganisms that are recognized as common pathogens of the human urogenital tract. To this end, the minimum inhibitory concentrations (MIC) of zinc gluconate and zinc lactate, with and without the presence of 10 molar equivalents of glycine, were determined by standard microbiological procedures for three organisms that are

of primary concern for the human urogenital tract, namely *Candida albicans, Gardnerella vaginalis,* and *Neisseria gonorrhea.* The results of this investigation are presented in Table 1.

TABLE 1

MIC (millimolar) of Zinc Salts in the Absence and in the Presence of 10 Molar Equivalents of Glycine

	ORGANISM		
Zinc Salt	*C. albicans*	*G. vaginalis*	*N. gonorrhea*
Gluconate	3.125	0.781	0.781
Gluconate and Glycine	1.562	0.781	0.781
Lactate	6.250	1.562	1.562
Lactate and Glycine	3.125	1.562	1.562

The results shown in Table 1 demonstrate that the presence of glycine does not stimulate the growth of any of the tested organisms, and in the case of *C. albicans* the presence of glycine appears to double the already considerable antimicrobial activity of the zinc salt by itself.

It is concluded that the presence of glycine in the zinc-containing formulations of the invention pose no risk of adverse bacteriological growth when the formulations are used on or in the human urogenital tract.

The anti-viral genital formulations of the invention include zinc gluconate as an anti-viral agent, and one or more select amino acids, in particular alanine, glycine, and/or lysine, to increase the solubility of the zinc gluconate in the formulations. It has been determined that each of alanine, glycine and

lysine act as a solubilizing agent for zinc gluconate in aqueous solutions (including gels) that are well-suited for use as lubricants during intercourse.

The addition of alanine, glycine, and/or lysine to an aqueous formulation containing zinc gluconate allows high quantities of the zinc gluconate (up to about 13%, on a weight per volume (w/v) basis) to become completely soluble in water or in aqueous gels. This completely overcomes and eliminates the problem of residual particles and grittiness, which (as set forth in the above-cited U.S. Patents to Kelly) would pose a serious risk of abrasion if zinc gluconate were used in a genital lubricant without a solubilizing agent as in the present invention.

In, addition to alanine, glycine, and/or lysine affecting the solubility of zinc gluconate in providing a genital formulation, a further benefit provided is that the amino acid improves both the odor and flavor of the formulation. The positive effect of certain amino acids on zinc gluconate as to taste is disclosed in U.S. Patent Nos. 4,684,528 and 4,758,439 to Godfrey.

Of the select amino acids, lysine is a preferred solubilizing agent for zinc gluconate in genital lubricant formulations since lysine reportedly has anti-herpetic activity in its own right, and can help to further reduce the risk of infection by genital herpes viruses. The anti-herpetic activities of lysine are discussed in articles such as Kagan, 1974[8]; Griffith et al, 1978[4], 1981[5], and 1987[6]; Milman et al, 1980[14]; Walsh et al, 1983[19]; Miller et al, 1984[13]; Thein et al, 1984[18]; and McCune et al, 1984[12]. It appears that the primary biochemical mechanism for the anti-herpetic activity of lysine involves its ability to competitively reduce the amount of arginine that is available to herpes viruses. Herpes viruses have unusually high quantities of arginine in their viral proteins, and it has been shown that lysine supplementation can help reduce the frequency and

severity of herpetic outbreaks in people who suffer from genital herpes or cold sores, especially if lysine supplements are also coupled with the reduced consumption of foods that are rich in arginine.

Accordingly, based on the discovery that lysine can also be used as a solubilizing agent for zinc gluconate, a combination of zinc gluconate and lysine offers a highly preferred anti-viral combination, in particular for use in genital lubricants, that can work through two different but compatible molecular mechanisms.

Molar ratios of amino acid to zinc gluconate within a range of about 1:1 to about 50:1 can substantially increase the solubility of zinc gluconate in an aqueous solution, and accordingly can be useful for genital lubricants as described herein. Optimal preferred molar ratios for any specific type of carrier substance (such as a gel containing a hydroxylated cellulose derivative and glycerin) can be determined using no more than routine experimentation, and are in the range of about 2:1 (which is likely to be necessary to impart complete solubility to the zinc gluconate) to about 30:1. Addition of even higher levels of alanine, glycine and/or lysine are not likely to be necessary to completely solubilize the zinc gluconate. However, as noted elsewhere, these amino acids (especially lysine, which has its own anti-herpetic activity) can be useful to enhance the overall performance of a gel, and can also function as flavor masking agents. Accordingly, addition of even higher molar ratios may be preferred to maximize such additional effects in various lubricant formulations.

Carrier Agents For
Providing Genital Formulations

The exact ingredients of a carrier for use with zinc gluconate and an alanine, glycine, and/or lysine solubilizing agent in providing a genital formulation are

not critical so long as the carrier mixture offers good lubricating characteristics and is physiologically safe and acceptable. The carrier is preferrably aqueous-based and must not irritate mucous membranes or other genital surfaces, even when rubbed in vigorously. It also must be free of anti-coagulants (such as heparin or dextran sulfate) or any other components that could pose a risk of adverse effects in a significant portion of the population, in a mixture that is used frequently and repeatedly, as with a lubricant. The carrier must also be free of transition metal ion complexing agents, such as ethylenediaminetetraacetic acid, citric acid or citrate ion, tartaric acid, sorbitol or mannitol, or any other known metal ion chelating agents, for their presence would make zinc unavailable as the free cation. Zinc availability is important for the invention to serve its primary intended function.

In one preferred embodiment, the lubricant formulations containing zinc gluconate and one or more select amino acids is in the form of aqueous gels, or other liquid or viscous semi-liquid formulations that are suitable for use with or without condoms. Aqueous gels that can be used with or without condoms generally contain:

a. water;

b. a thickening agent, such as cellulose (or a chemically modified derivative of cellulose, such as hydroxyethyl- or hydroxymethyl-cellulose), acacia, agar, alginate, carrageenan, gum tragacanth, xanthan gum, collagen, carboxypolymethylene, glyceryl monostearate, polyvinylpyrrolidone, and polyacrylamide; and,

c. a lubricating agent, such as glycerin, propylene glycol, polyethylene glycol, polypropylene glycol, polyisobutene, polyoxyethylene, behenic acid, behenyl alcohol, and polydimethylsiloxane.

The thickening and lubricating agents listed above are not biologically active, and basically serve as

non-toxic, non-irritating carrier substances. Other pharmaceutically safe conventional thickening agents and lubricating agents are also useful.

As used herein, "lubricating agent" refers to a component which is incorporated into a genital lubricant formulation for the purpose of reducing friction during intercourse. Although any liquid (including water) can sometimes function as a "lubricant" in the broadest sense of the word, four characteristics distinguish a "lubricating agent," as that term is used herein, from water and other liquids that do not have the characteristics necessary for effective lubrication during sexual intercourse: (1) a proper lubricating agent is substantially more viscous than water and feels slippery when rubbed between two skin surfaces; (2) a lubricating agent should have an affinity for human skin, and when applied to skin, it should spread smoothly and evenly across the contacted area; (3) a lubricating agent should remain in contact with the skin, clinging to it in a more substantial manner than water, which is easily wiped away; and, (4) a lubricating agent should have a low level of volatility, and should not evaporate quickly. The foregoing characteristics can be easily recognized and understood on a practical level by rubbing a conventional lubricating agent (such as glycerin, mineral oil, or a condom lubricant) between the fingers. The nature and the durability of the lubrication, and the differences between such agents and less suitable liquids such as water, are readily apparent.

In addition, in order to be physiologically acceptable, a selected lubricating agent should not cause any significant adverse effects (such as irritation, tenderness, swelling, redness, or skin discoloration), and must not pose a significant risk as a carcinogen or teratogen. Further, in contrast to non-physiological lubricants (such as mineral oil), physiologically acceptable lubricating agents should be gradually broken

down into innocuous substances in the body if they are absorbed by tissue to a significant degree through the skin or mucous membranes, or they should be of a nature that allows them to be secreted by the vagina and washed cleanly from the skin so that they will not clog the pores in mucous membranes or dermal layers.

Several lubricating agents which are used in commercially available genital lubricants satisfy these criteria, including glycerin (also called glycerine, glycerol, 1,2,3-propanetriol, and trihydroxypropane) and certain types of polyethylene glycol (PEG), such as PEG 200 or PEG 400 (the numbers indicate different molecular weight averages). Various other polymers (such as polypropylene glycol, polyisobutene, and polyoxyethylene) and behenic acid and behenyl alcohol are also useful as lubricants in cosmetics and other formulations that contact the skin. In addition, some sugar alcohols, such as sorbitol, and some silicon compounds, such as polydimethylsiloxane, are also used as condom lubricants or other skin-contacting lubricating agents. It is to be noted that sorbitol and all other straight chain saturated sugars, including mannitol, hydrogenated starches and hydrolyzed hydrogenated starches, are to be avoided in zinc-containing lubricants because of their propensity to bind and inactivate zinc ions which must be substantially free for the purposes of the invention.

Since glycerin, propylene glycol, polyethylene glycol, and polypropylene glycol have long been used in genital lubricants and other skin-contacting formulations with no adverse effects, they are preferred for use as lubricating agents in the anti-viral genital formulations of the invention. The suitability of any other lubricating agent for use as described herein can be determined through routine experimentation in humans to ensure that it will not cause irritation or other adverse effects, and in *in vitro* cell culture tests and *in vivo* lab animal tests (as described in U.S. Patent No.

5,208,031) to ensure that the candidate lubricating agent does not substantially reduce the anti-viral effectiveness of a formulation containing zinc gluconate and one or more select amino acid.

Chemically treated derivatives of cellulose (such as hydroxyethyl- or hydroxymethyl-cellulose) are widely used as thickening agents in gels that are designed for use as genital lubricants during intercourse. Other thickening agents which have been used in skin-contacting compounds, and are potentially useful in zinc-containing genital lubricant formulations, include acacia, agar, alginate, carrageenan, gum tragacanth, xanthan gum, collagen, carboxypolymethylene, glyceryl monostearate, polyvinylpyrrolidone, and polyacrylamide.

Other components, including preservatives (such as chlorhexidine gluconate or methyl paraben), anti-crystallization agents (such as glucono-delta-lactone), fragrances, coloring agents, alkaline or acidic or buffering agents to maintain the proper pH, and soothing or anti-swelling agents (such as lanolin, cocoa butter, aloe vera extract, or hydrocortisone) can be added to the formulations described herein, so long as any such additive, at the relevant concentration, does not seriously impede the anti-viral activity of the zinc due to reactions such as chelation, and so long as it does not irritate or have other adverse effects on the genitals.

Use of Two Zinc Salts in
Anti-viral Genital Formulations

In an alternate preferred embodiment, anti-viral genital formulations for use as described herein can contain two zinc salts. One zinc salt will be zinc gluconate, with alanine, glycine, and/or lysine as an additive to increase its solubility. The second zinc salt can be any other zinc salt that is pharmacologically acceptable for such use, i.e., it must be water-soluble,

non-irritating, non-toxic, etc. when used in a genital formulation during intercourse.

Due to the nature of chemical equilibria in fluid systems, the addition of a relatively large quantity of an exogenous compound may impose a higher level of disruption of the chemical homeostasis inside a vagina or urethra, compared to the addition of smaller quantities of two different compounds. By way of illustration, inserting 100 millimoles of zinc gluconate into a vagina is likely to cause more disruption of the chemical equilibria than inserting only 50 millimoles of zinc gluconate and 50 millimoles of a different salt such as zinc lactate.

In addition, it is believed that lactate ions are completely benign and well-tolerated inside a vagina. The normal and natural pH inside a healthy vagina is about 5, which is highly acidic compared to most other bodily fluids. That high level of acidity is largely due to the presence of lactic acid inside the vagina. This high level of acidity is completely healthy. Among other things, the acidity helps the vagina resist infection by any number of opportunistic microbes which cannot reproduce well in acidic environments.

Accordingly, the mucous membranes and epithelial cells inside the vagina are completely adapted to function normally in the presence of high concentrations of lactate ions. These ions do not exist in static, unchanging form. Instead, the ions are constantly being generated anew and are constantly being metabolized into other compounds by numerous cellular and extra-cellular processes. Like the cells and membranes themselves, these ongoing processes are well-adapted to function in the presence of lactate ions. Accordingly, it is believed that zinc lactate is well-suited and completely benign if used in a vaginal lubricant.

For the reasons described above, a combination of zinc lactate and zinc gluconate (together with

alanine, glycine, and/or lysine as a solubilizing agent for the zinc gluconate) is likely to offer a preferred formulation for an anti-viral genital lubricant. Additionally or alternately, various other zinc salts (such as zinc acetate, zinc propionate, or any of the other salts listed or described in the various above-cited U.S. Patents to Kelly) also are good candidates for evaluation and possible use in combination with zinc gluconate in genital formulations as described herein.

In addition, various other zinc salts have also been evaluated for use as anti-viral additives in genital formulations. Any salt which has a useful combination of the following three traits is a suitable candidate: (1) adequate solubility in water in the presence of any solubilizing agents; (2) sufficiently high levels of ionic dissociation to allow it to release substantial quantities of free zinc ions, and (3) freedom from other traits that would be undesirable in a genital formulation, such as an unpleasant odor. In general, such salts include any of numerous salts formed from carboxylic acids having relatively low molecular weights, such as zinc propionate, zinc acetate, zinc glycerate, and zinc glycolate. Reported solubility values and pK levels (which reflect ionic dissociation) for these salts are listed below in Table 2. The list in Table 2 is not exclusive. Numerous other potentially suitable organic salts of zinc, such as zinc malonate and other dicarboxylic salts, are also known and can be evaluated for use herein if desired.

TABLE 2

PROPERTIES OF VARIOUS ORGANIC ACID SALTS OF ZINC

Salt	Solubility (grams/ liter)	Molecular weight	Molar solubility (moles/ liter)	Reported pK values
Zinc acetate	300(25°C)	183.4	1.64	1.03
Zinc propionate	320(15°C)	211.5	1.51	1.01
Zinc gluconate	127(25°C)	455.7	0.28	1.70
Zinc glycerate	NA	275.6	NA	1.80
Zinc glycolate	NA	215.5	NA	1.92
Zinc lactate	57	279.5	0.20	1.86

Sources: Sillen and Martell, 1964 and 1971[17]; Lide, 1990[10]; Linke, 1965[11]; Cannan and Kibrick, 1938[3].

EXAMPLES

Example 1: Preparation of Lubricant Jelly containing Zinc Gluconate solubilized with Glycine

A batch of 90.0 grams of lubricant gel base was prepared from 0.20 g guar gum, 0.10 g methyl paraben, 5. 0 g hydroxymethyl cellulose, 0.30 g glucono-delta-lactone, 2.8 g glycerine, 0.50 g chlorhexidine gluconate, and 81.1 g of deionized water. A clear solution containing 510 mg (1.00 millimole) of zinc gluconate trihydrate and 750 mg (10.0 millimoles) of glycine in 8.74 g of deionized water was prepared by gentle heating. This solution, at 40°C, was added with vigorous stirring to the 90.0 g of lubricant gel base. A clear, viscous gel was obtained. By tactile comparison, it was judged to be very similar in lubricating properties to the commercial product without zinc, K-Y Lubricating Jelly™. It was calculated to contain dissolved zinc at a 10.0 millimolar concentration and glycine at a 0.100 molar concentration.

Example 2: Preparation and Testing of Lubricating Jelly Containing Zinc Gluconate and Glycine

Since K-Y Lubricating Jelly™ (Johnson & Johnson, New Brunswick, NJ) and its generic equivalents (available in numerous drugstore and discount store chains) have a long and satisfactory history of safe and effective use as lubricants during sexual intercourse, the final lubricants described herein were intended to contain the same carrier ingredients, in the same concentrations, as K-Y Lubricating Jelly. This was accomplished by using K-Y Lubricating Jelly taken directly from a tube of K-Y Lubricating Jelly purchased at a drugstore, as a starting material. 67.5 grams of gel was removed from the tube and put in a shallow glass dish which in turn was placed inside a desiccator device. The gel was heated to about 63°C (about 145°F) for 4 hours while a small fan blew filtered air across the plate. After 4 hours, the weight of the remaining gel was 26.7 g, which indicated that about 60% of the weight as water (40.8 g) had been evaporated. The residue was sticky and highly viscous.

To provide the proper amount of water to reconstitute the gel back to its original water content, 41 ml of distilled deionized water was used. 342.7 mg of zinc gluconate trihydrate and 877.3 mg of glycine were dissolved in this water, and the mixture was added to the desiccated gel residue. Within a few minutes of stirring using a small metal spatula, the gel had returned to its original smooth consistency with no apparent change in viscosity or other characteristics. The final zinc gluconate content in this gel was 10 millimolar (= 0.06538 percent, by weight). It was loaded back into the tube for handling and testing purposes by cutting open the crimped end of the tube, spooning the zinc gluconate/glycine gel back into the tube through the open end, and resealing the end of the tube using adhesive tape.

This gel was subsequently used as a genital lubricant during intercourse by a married couple. When finished, both people wiped off any excess with a tissue, but did not shower or wash off until the following day. The lubricant gel caused no irritation or other adverse effects of any sort. It had a neutral or slightly sweet taste and no noticeable odor. It was regarded by both the male and female as entirely satisfactory, comfortable and pleasant, in all respects.

Example 3: Preparation and Testing of Zinc Gluconate With Lysine

A lubricant gel (designated as ZnGlu/Lys) containing zinc gluconate with lysine as a solubilizing agent was prepared. 80.0 g of K-Y Lubricating Jelly was evaporated to 38.6 g in a desiccator, as described above. An aqueous solution containing 41.5 ml of distilled water, 612 mg zinc gluconate trihydrate (1.2 millimoles), 450 mg L-lysine monohydrochloride (2.46 millimoles), 360 mg glycine (4.80 millimoles), and 202 mg $NaHCO_3$ (2.40 millimoles) was prepared by stirring and filtering at room temperature. The filtrate was added to the desiccated K-Y Lubricating Jelly to bring the weight back up to the original 80.0 grams. The mixture was hand-stirred periodically and allowed to sit in a closed container. After several hours, its original consistency had been restored.

The quantities specified above provided final concentrations of 15 mM zinc gluconate, 30 mM lysine, 60 mM glycine, and 30 mM NaCl. The 15 mM zinc gluconate concentration was chosen because that concentration was reported to completely block herpes simplex virus replication by Kumel et al, 1990[9].

The reconstituted gel was reloaded into the tube and used as a genital lubricant during intercourse by a married couple. When finished, both people wiped off any excess with a tissue, but did not shower or wash off until the following day. The ZnGlu/Lys lubricant caused

no irritation or other adverse effects of any sort. It had a neutral or slightly sweet taste and no noticeable odor. It was regarded by both the male and female as entirely satisfactory in all respects.

Example 4: Preparation of Lubricant Gel with Zinc Gluconate and L-Alanine

A sample of K-Y Lubricating Jelly™ weighing 85.2 g was evaporated to a residual weight of 55.1 g by gentle heating in a stream of filtered air. A clear solution of 725 mg of zinc gluconate trihydrate (1.42 millimole) and 1.584 g of L-alanine (17.78 millimole) in 27.8 g of purified, deionized water was prepared at room temperature and added to the partially dehydrated gel. Manual stirring with a glass rod for 10 minutes produced a clear gel with the same viscosity and lubricating properties as the gel starting material. Triplicate quantitative analysis of this product by atomic absorption spectroscopy (AAS) found 1.113, 1.087, and 1.078 mg of zinc per gram of gel, a mean zinc content of 1.093 mg/g corresponding to a 16.7 millimolar concentration of zinc ion.

Example 5: Preparation of Lubricant Gel with Zinc Gluconate, Glycine, and L-Alanine

A lubricant gel was prepared by evaporating 74.8 g of K-Y Lubricating Jelly™ to 40.2 g and reconstituting as in Example 4 with a solution of 387 mg of zinc gluconate trihydrate (0.759 millimole), 300 mg of glycine (4.00 millimole), and 321 mg of L-alanine (3.60 millimole) in 333.6 g of purified water. The clear gel product was found by AAS to contain 0.638 mg of zinc per gram of gel, a 9.8 millimolar concentration.

Thus, a new genital formulation, and method of providing the formulation, containing zinc gluconate as an anti-viral agent and one or more select amino acid (glycine, alanine and/or lysine) as a solubilizing agent for the zinc gluconate has been shown and described. Although the invention has been exemplified for purposes of illustration and description by reference to certain

specific embodiments, it will be apparent to one skilled in the art that various modifications, alterations, and equivalents of the illustrated examples are possible. Any such changes which derive directly from the teachings herein, and which do not depart from the spirit and scope of the invention, are deemed to be encompassed by the invention.

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IT IS CLAIMED:

1. A liquefied formulation for application to genitals for use prior to and during intercourse comprising:

(a) zinc gluconate present at an effective concentration to reduce infectivity of at least one sexually transmitted virus during use of the formulation;

(b) at least one amino acid selected from the group consisting of L-alanine, D,L-alanine, glycine, L-lysine and D,L-lysine, present at an effective concentration to solubilize said zinc gluconate; and

(c) a pharmaceutically acceptable carrier for said zinc gluconate and said at least one amino acid;

wherein the liquefied formulation is physiologically acceptable, and has a sufficient viscosity that serves to allow retention of said formulation on the genitals during intercourse.

2. The liquefied formulation of Claim 1 wherein the zinc gluconate is present at a concentration of from about 0.10 millimolar to about 200 millimolar.

3. The liquefied formulation of Claim 1 wherein the at least one amino acid is glycine and said glycine is present at a molar ratio to said zinc gluconate of from about 1 to about 50.

4. The liquefied formulation of Claim 1 wherein the at least one amino acid is L-alanine and/or D,L-alanine, and said L-alanine and/or said D,L-alanine is present at a molar ratio to said zinc gluconate of from about 1 to about 50.

5. The liquefied formulation of Claim 1 wherein the at least one amino acid is L-lysine and/or D,L-lysine, and said L-lysine and/or said D,L-lysine is present at a molar ratio to said zinc gluconate of from about 1 to about 50.

6. The liquefied formulation of Claim 1 further comprising a zinc salt, other than said zinc gluconate, which is water-soluble.

7. The liquefied formulation of Claim 6 wherein said zinc salt is zinc lactate.

8. The liquefied formulation of Claim 6 wherein the zinc salt is selected from the group consisting of zinc propionate, zinc acetate, zinc glycerate, and zinc glycolate.

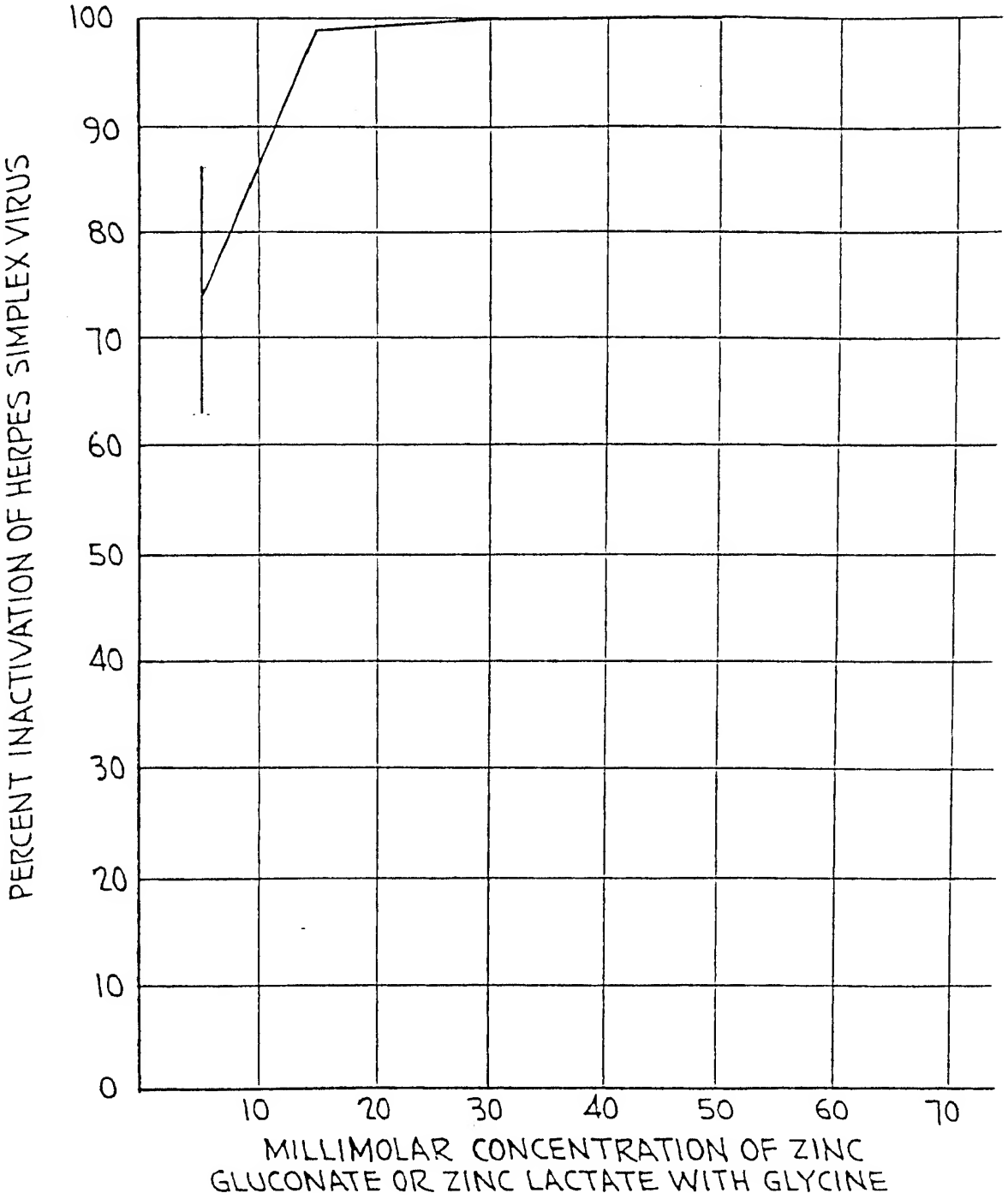
9. The liquified formulation of Claim 6 wherein said zinc gluconate is present at a concentration of from about 0.01 to about 100 millimolar.

10. The liquefied formulation of Claim 6 wherein said at least one amino acid is present at a molar ratio to a sum of said zinc gluconate and said zinc salt of from about 1 to about 50.

11. The liquefied formulation of Claim 1 wherein said formulation is a gel.

12. The liquefied formulation of Claim 1 wherein said carrier includes water.

13. A method of reducing risk of infection by at least one sexually transmitted virus, comprising applying a liquefied formulation according to claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 to at least one genital surface prior to sexual intercourse.



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(54) Title: SELECT AMINO ACIDS AS ZINC-SOLUBILIZING AGENTS IN ANTI-VIRAL GENITAL FORMULATIONS

(57) Abstract: Formulations including zinc gluconate and select amino acids for use on genital surfaces to help prevent the spread of sexually transmitted diseases are disclosed. The select amino acids are glycine, arginine, and/or lysine. These formulations are generally applied shortly before sexual intercourse. When used in this manner, the formulations provide a non-toxic, non-irritating chemical protective layer that reduces the risk of viral transmission from an infected person to an uninfected person.

INTERNATIONAL SEARCH REPORT

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: compounds and anti-std use

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,070,080 A (FAHIM) 03 December 1991, see entire patent	1-6, 9-12
Y	US 5,208,031 A (KELLY) 04 May 1993, see entire document	1-13
Y	US 4,424,232 A (PARKINSON) 03 January 1984, see entire document	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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